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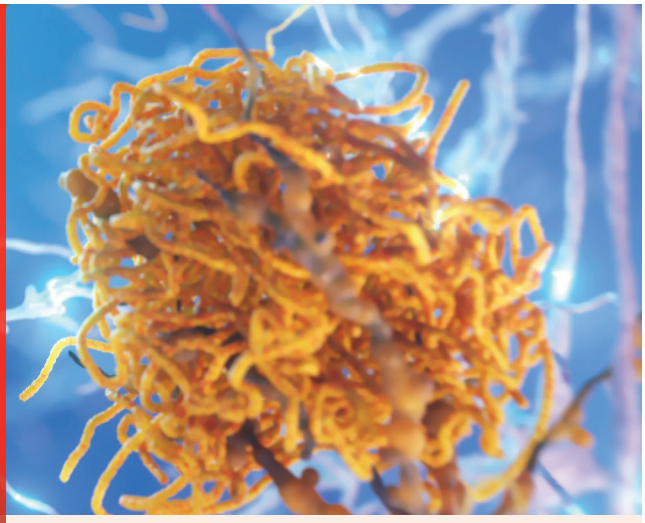
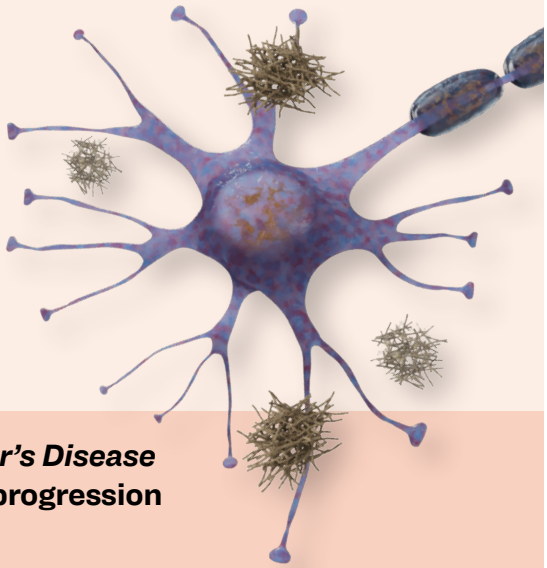
What do amyloid and tau biomarkers tell us about cognitive decline in asymptomatic older adults?



- Alzheimer's disease (AD) is a progressive neurodegenerative disorder associated with cognitive, functional, and behavioral impairments.[1,2]
- The hallmark features of AD include β-amyloid plaques and tau neurofibrillary tangles which are thought to drive neurodegeneration.[1-3]
- AD-related pathology accumulates decades before cognitive symptoms appear in a phase of the disease called preclinical AD.[1,2,4]
  - These individuals are at high risk for developing cognitive symptoms



A recent study* published in the *Journal of Prevention of Alzheimer's Disease* reported on the relationship between AD-related biomarkers and progression from preclinical to symptomatic stages.[5]

Study design[5†]

The study used data from the Phase 3 Anti-Amyloid Treatment in Asymptomatic Alzheimer's disease (A4) trial as well as its companion study, the Longitudinal Evaluation of Amyloid and Neurodegeneration Risk (LEARN) study.

Together, these studies enrolled over 1700 participants ages 65-85 who:

- Were cognitively unimpaired at baseline
- Were in overall good health
- Had a study partner familiar with their cognitive function
- Had varying levels of amyloid pathology measured via baseline PET

Elevated Amyloid	Negative Amyloid
A4 Trial	LEARN Study

Researchers explored whether baseline levels of amyloid PET, plasma P-tau217, and tau PET (subset of participants) could predict cognitive and functional outcomes over ~4.5 years.

More on biomarkers[4,5]

Amyloid PET imaging

- Measures amyloid plaques in the brain; abnormal amyloid plaque deposition is thought to be the first neuropathological sign of AD

Plasma P-tau217

- **Primarily reflects amyloid plaque burden**
- Also reflects an early stage of tau phosphorylation contributing to the misfolding process that results in tau neurofibrillary tangle formation
  - May also reflect the degree to which amyloid is triggering downstream effects like tauopathy

Tau PET imaging

- Measures aggregated tau neurofibrillary tangles in the brain, which are thought to occur later in the process of AD; abnormal Tau PET is closely coupled with clinical symptoms and neurodegeneration

Results[5]

Select baseline participant characteristics for participants with available P-tau217 data

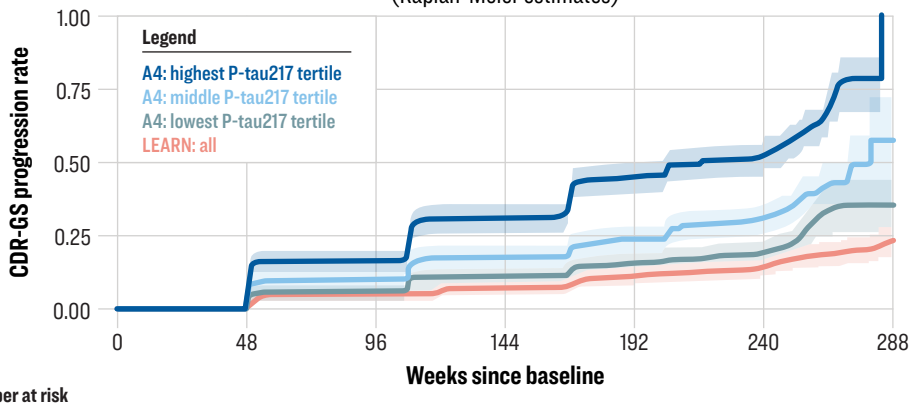
	A4 Trial (N=1056)	LEARN Study (N=469)
Age (years)	**71.9** (4.8)	**70.5** (4.3)
Female sex	**617** (58.4%)	**289** (61.6%)
Family history	**792** (75.0%)	**308** (65.7%)
Amyloid PET (Centiloids)	**66.2** (32.7)	**4.7** (12.4)
Plasma P-tau217	**0.3** (0.2)	**0.2** (0.1)

Key findings[5]

~50% **of people with preclinical AD,** as indicated via higher levels of AD-related biomarkers, progressed to the symptomatic stages of AD within 5 years.

- The majority of participants without AD-related pathology did not exhibit symptomatic progression

Clinical Dementia Rating-Global Score (CDR-GS) Progression by Plasma P-tau217
(Kaplan-Meier estimates)



Number at risk							
>0.28	357	337	278	219	167	131	0
0.2 to 0.28	354	340	292	254	229	181	2
<0.2	354	343	308	273	243	202	1
LEARN	506	492	442	400	337	285	77

Figure modified from Sperling RA, et al.[5]

Across the entire cohort, baseline plasma P-tau217 was the strongest predictor of cognitive decline.

- In a subset of participants with tau PET imaging, neocortical tau was the strongest predictor of cognitive decline, showing that tau deposition is related to clinical deterioration

The study reported that cognitively unimpaired individuals with preclinical AD and higher levels of biomarkers such as plasma P-tau217 *showed a greater risk of progressing to symptomatic AD within 5 years.*

Limitations[5]

- Participants in the study may not represent a generalizable older population. They were generally in good health, volunteered and met screening criteria for the A4 clinical trial, were willing to commit to multiple visits over several years, had higher rates of family history of dementia than typical, and were predominantly White and not Hispanic or Latino
- Participants were also aware of their amyloid PET status (elevated vs not elevated), which may have influenced assessments

*This study was funded by the National Institute of Aging of the National Institutes of Health (R01 AG063689, U19AG010483, and U24AG057437), Eli Lilly (also the supplier of active medication and placebo), the Alzheimer's Association, the Accelerating Medicines Partnership through the Foundation for the National Institutes of Health, the GHR Foundation, the Davis Alzheimer Prevention Program, the Yugilbar Foundation, an anonymous foundation, and additional private donors to Brigham and Women's Hospital, with in-kind support from Avid Radiopharmaceuticals, Cogstate, Albert Einstein College of Medicine and the Foundation for Neurologic Diseases. †In the A4 study, participants were randomly assigned (1:1) to receive either a placebo (n=583) or intravenous infusions of an amyloid-targeting antibody (n=564). As no significant treatment effects were seen in the A4 study, the treatment arms were combined for analyses, but treatment assignment was considered as a co-variate. In the LEARN study, participants (n=553) did not receive any intervention but underwent the same assessments as those in the A4 study.

PET=positron emission tomography.

1. Alzheimer's Association. *Alzheimers Dement*. 2025;21(4):e70235. **2.** Porsteinsson AP, et al. *J Prev Alz Dis*. 2021;3(8):371-386. **3.** Raskin J, et al. *Curr Alzheimer Res*. 2015;12(8):712-722. **4.** Jack CR Jr, et al. *Alzheimers Dement*. 2024;20(8):5143-5169. **5.** Sperling RA, et al. *J Prev Alz Dis*. 2024;4(11):802-813.

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